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## **APPENDIX D**

# **International Preliminary Examination Report**

# PATENT COOPERATION TREATY

## PCT



### INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2003946-0018		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/US 03/07377		International filing date (day/month/year) 07.03.2003	Priority date (day/month/year) 08.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D313/00			
Applicant EISAI CO. LTD. et al.			

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 44 sheets.</p>	
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>	

Date of submission of the demand 25.09.2003	Date of completion of this report 29.06.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Kirsch, C Telephone No. +49 89 2399-2191 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/US 03/07377**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-377

as originally filed

**Claims, Numbers**

12-19, 53-58, 59 (part), 97-105 as originally filed

1-11, 20-52, 59 (part), 60-96, received on 30.04.2004 with letter of 28.04.2004  
106-126

**Drawings, Sheets**

1/9-9/9

as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

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5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

**see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 84-126

because:

☒ the said international application, or the said claims Nos. 84-126 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	22-36,66-80,108-118
	No: Claims	1-21,37-65, 81-107,119-126
Inventive step (IS)	Yes: Claims	
	No: Claims	1-126
Industrial applicability (IA)	Yes: Claims	1-83
	No: Claims	

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2. Citations and explanations  
**see separate sheet**

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International application No. PCT/US03/07377

Reference is made to the following documents:

- D1: EP-A-0 606 044
- D2: WO96/13259
- D3: WO00/38674
- D4: Agastuma T. et al., Chem. Pharm. Bull., 1993, 41(2), 373-375
- D5: Takehana K. et al., Biochem. Biophys. Res. Comm., 199, 257, 19-23
- D6: WO02/48136 (P-document)

Document D6 published 20.06.2002 with filing date of 13.12.2001 and claiming priority date of 14.12.2000 has been found in a search of the state of the art in accordance with Art. 33(2) and (3) and rule 64.3 PCT. This document will not be taken into account in international phase, however, the attention of the applicant is drawn to the fact that it may prove relevant when assessing novelty and inventive step in the regional phases.

The present application deals with macrolactone analogs of zearalenone having (Z)-configuration at C-5-C-6 and (S)-configuration at C-8 and their use as antiinflammatory, immunosuppressive, anticancer and antiageing agents.

**Re Item I**

**Basis of the report**

Excluding protection for part of the subject-matter of the claimed invention, as covered by the application as filed, by disclaiming a certain anticipation in the state of the art is acceptable under the terms of Article 34(2)b PCT only if the following conditions are met:

(i) the subject-matter disclaimed must be precisely defined and strictly limited to the actual scope of the anticipation, and

(ii) said anticipation must be a so-called "chance anticipation", which means that it would be regarded as accidentally falling within the terms of the claim(s) of the application.

Condition (ii) specifically refers to cases where the anticipation is of a chance nature in that

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what is disclosed in the prior document could accidentally fall within the wording of the claim(s) of the application to be assessed for novelty without there being a common or related technical field, or a common technical problem or solution. In other words, the prior document must form part of an entirely remote and unrelated state of the art which the skilled person, faced with the assessment of inventive step, would normally never take into consideration.

When carrying out the comparison in the present case it is found that the relevant disclosure in citations D1-D5 relates to macrolactone analogs of zearalenone and their use as antiinflammatory, or anticancer agents and, accordingly, to exactly the same technical field solving exactly the same technical problem as the claimed invention. Since the state of the art referred to in citations D1-D5 is highly relevant to the claimed subject-matter in the application, condition (ii) is clearly not met. Accordingly, the disclaimer is not allowable within the framework of Article 34(2)b PCT and, consequently, the amendment as a whole is not acceptable. Therefore, this report has been drafted as if no disclaimer has been introduced.

The expressions "pharmaceutically acceptable derivatives" and "lower alkyl" have been clarified in the light of the description. Support for these modifications can be found in paragraphs [0087] and [0090] respectively. These amendments are in accordance with the requirements of Art. 34(2)b PCT.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 84-126 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Document D1 describes macrolactone analogs of zearalenone useful as cytokine release inhibitors and IL-1 antagonists for the treatment of inflammatory disorders. Formula (I) of D1 overlaps with the definition given in the present application where a-b is a cis-C=C, C is C=O and d is (S)-CH(OR). Such structural features are disclosed in claims 2-4 and 6 and are illustrated in formula (I'), examples 8 and 10. Since no structural element common to all the possibilities comprised in this overlap could be identified, the present claimed subject-matter cannot be considered novel over D1 (Art. 33(2) PCT).

Document D2 discloses macrolactone analogs of zearalenone which inhibit protein kinases such as tyrosine kinases and can therefore be used in the treatment of various diseases including cancers and restenosis (see p. 12-14). On the basis of claim 1, it turns out that there is an overlap between the claimed subject-matter and the teaching of D2 when the configuration at positions 3, 5-6 and 8 in formula (I) of D2 are as described in the present application. These features are disclosed in claims 9 and 10 and on p. 9, I. 6-7 as well as in compound C292 which falls within the scope of the present invention.

Consequently, no new technical element common to the compounds of the present application which fall within the overlap and which can be regarded as adding a new element to the state of the art could be identified so far. Since, this new technical feature, which is necessary to established novelty, fails, this overlap is considered identical to what has already been disclosed in D2 (Art. 33(2) PCT).

The content of D2 is neither limited to its examples nor to the preferred embodiments disclosed therein. The content of D2 should be regarded as a whole and all the information contained therein is state of the art in the sense of Art. 33(2) PCT.

Document D3 reveals zearalenone derivatives which affect mRNA stability and are useful in the treatment of cancer and inflammatory diseases. Formula (II) of D3 overlaps with formula (I) according to the present application when a-b is a cis-C=C, C is C=O and d is (S)-CH(OR). These structural features are described on p. 6, last 2 lines and in formula (III). Since no new technical element which could provide a contribution over the prior art could be identified, the subject-matter of the present application is considered to lack novelty (Art. 33(2) PCT). In order to established novelty, the applicant should identify a new structural element which is common to all the alternatives comprised in the overlap and which is not disclosed in the prior art.

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Document D4 discloses the corrected structure hypothemycin which exhibit antiproliferative activity on P388 cell lines and the synthesis of analogs thereof. Hypothemycin (1) as well as its triacetate (3) fall within the scope of claim 1. Claim 1 lacks novelty with regard to document D4 (Art. 33(2) PCT).

Document D5 deals with the biological activity of radicicol related compounds and especially their mechanism of action on cancer cell lines. The compounds 87-250904-F1 and LL-Z1640-2 both fall within the scope of the present invention. The subject-matter of claim 1 is not novel with regard to the disclosure of D5 (Art. 33(2) PCT).

2. The only structural element common to all the compounds claimed is the presence of a zearalenone core structure with a cis double at C-5-C-6 and (S)-configuration at C-8. Such a structural feature is already disclosed in documents D1 to D5 for compounds which exhibit the same biological activity. Since the common feature is not novel, it cannot represent the single inventive concept which could have linked the different claimed subject-matters together.

The technical relationship between the different subject-matters of claims 1-126 required by rule 13.1 PCT is missing and the requirement for unity of invention does not seem to be fulfilled.

3. Document D6 describes the use of zearalenone derivatives as keratinocytes proliferation inhibitors in the treatment or the prevention of skin diseases. The compounds of formula (1), (4), (8)-(9) and (11) differ from the present claimed subject-matter due to the absence of specific configurations for the chiral carbon atoms at positions 3 and 8. Novelty is acknowledged with regard to document D6 (Art. 33(2) PCT).
4. Documents D1 to D5, which are considered to represent the most relevant state of the art, disclose macrolactone analogs of zearalenone and their use in the treatment of various diseases such as cancer and inflammatory disorders.

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The problem to be solved by the present application may be considered as the provision of zearalenone derivatives for use as pharmaceutical agents.

Since zearalenone derivatives and their use as anticancer and antiinflammatory agents is already known from D1 to D5, the subject-matter cannot be considered inventive with regard to the disclosure of the prior art documents (Art. 33(3) PCT). Having regard to the similar compounds of D1 to D5, the problem may be reformulated as consisting in the obtention of further zearalenone derivatives for use as pharmaceutical agents with unexpected properties. Since no comparative data which could illustrate the presence of such properties for the claimed compounds are available, the problem has not been solved and inventive step cannot be acknowledged (Art. 33(3) PCT).

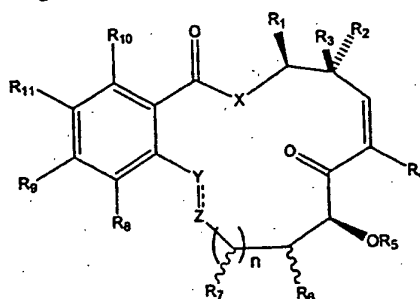
5. For the assessment of the present claims 84-126 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
6. The breadth of the claims should be such that it represents a reasonable generalisation over the examples provided (cf. Guidelines C-III, 6.2 and C-II, 4.9), and especially such that every compound falling within its scope actually provides a solution to the problem underlying the invention.

In the present case, the definitions "(hetero)aliphatic", "(hetero)alicyclic", "(hetero)aryl", "protected hydroxyl or amino", "alkyloxy", etc. used in the claims without precision about the number of carbon atoms or of heteroatoms, the size of the cycles or the kind of substituents, is vague and imprecise and could comprise compounds which would not exhibit the claimed activity (Art. 33(3) PCT).

## CLAIMS

We claim:

1. A compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

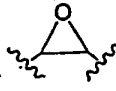
$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond;

with the proviso that when  $n$  is 1;  $X$  is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $R_9$  is OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $R_4$  is hydrogen;  $R_{10}$  and  $R_8$  are independently OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$  or  $-CH=CH-$ ;
- (ii)  $R_4$  and  $R_8$  are each hydrogen;  $R_{10}$  is OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CHR^YCHR^Z-$ ,  $-CH=CH-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl; and
- (iii)  $R_4$  and  $R_{10}$  are each hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_8$  is hydrogen, OH, halogen,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$ ,  $-CH=CH-$  or  $-C(=O)CH_2-$ .

2. The compound of claim 1, where the following groups do not occur simultaneously as defined:

X is oxygen,

$R_1$  is methyl,

$R_2$  and  $R_3$  are each hydrogen,

$R_4$  is hydrogen,

$R_5$  is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkanoyl,

$R_6$  is  $OR'$ , where  $R'$  is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkanoyl with S-configuration,

$R_7$  is hydrogen,

Y and Z together represent  $-CHR_{17}-CHR_{18}-$  or  $-CR_{17}=CR_{18}-$ , wherein

$R_{17}$  and  $R_{18}$  are independently hydrogen, or when Y and Z are  $-CHR_{17}-$

$CHR_{18}$ ,  $R_{17}$  and  $R_{18}$  taken together are  $-O-$ ;

$R_8$  is hydrogen or  $OR'$ , where  $R'$  is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkanoyl,

$R_9$  is  $OR'$ , where  $R'$  is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkanoyl,

$R_{10}$  is  $OR''$ , where  $R''$  is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkanoyl; and

$R^{11}$  is hydrogen.

3. The compound of claim 1, wherein:

$R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

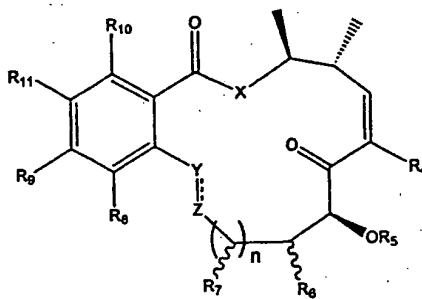
$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $C_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond.

4. The compound of claim 3, where  $X$  is oxygen and  $n$  is 1.
5. The compound of claim 3, where  $R_4$  is halogen.
6. The compound of claim 3, where  $R_4$  is fluorine.
7. The compound of claim 3, where  $Y$  and  $Z$  together represent  $-CH=CH-$ .
8. The compound of claim 3, where  $Y$  and  $Z$  together represent trans  $-CH=CH-$ .

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9. The compound of claim 3, wherein  $R_1$  and  $R_2$  are each methyl and  $R_3$  is hydrogen and the compound has the structure:



wherein  $R_4$ - $R_{11}$ ,  $n$ ,  $X$ ,  $Y$  and  $Z$  are as defined in claim 3.

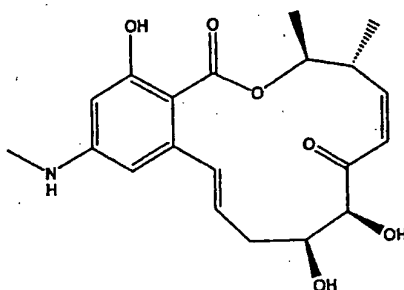
10. The compound of claim 9, wherein  $X$  is oxygen and  $n$  is 1.
11. The compound of claim 9, wherein  $R_4$  is halogen.

AMENDED SHEET

20. The compound of claim 15, wherein X is oxygen, n is 1, R<sub>1</sub> and R<sub>2</sub> are each methyl, R<sub>3</sub> is hydrogen, R<sub>4</sub> is halogen, and Y and Z together represent -CH=CH-.

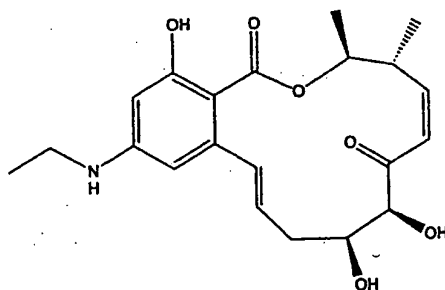
21. The compound of claim 18 or 20, wherein -CH=CH- is trans.

22. A compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

23. A compound having the structure:

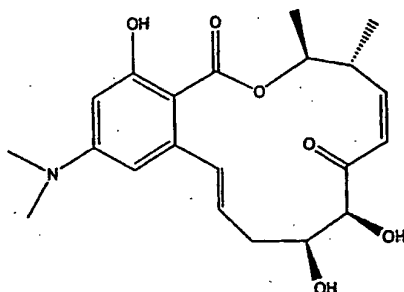


or pharmaceutically acceptable salt, ester, or salt of ester thereof.

24. A compound having the structure:

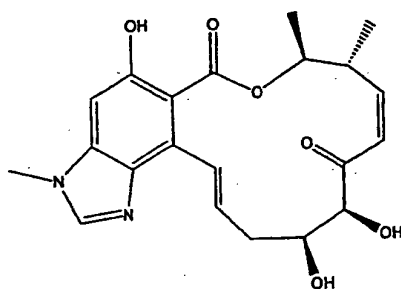
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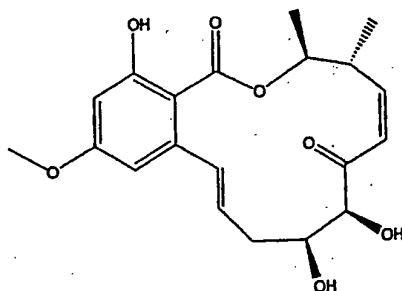
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

25. A compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

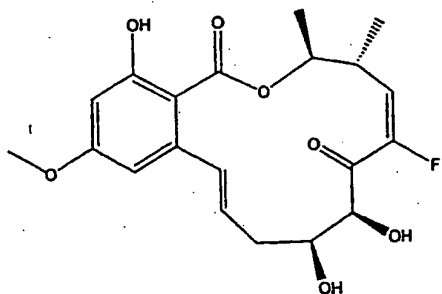
26. A compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

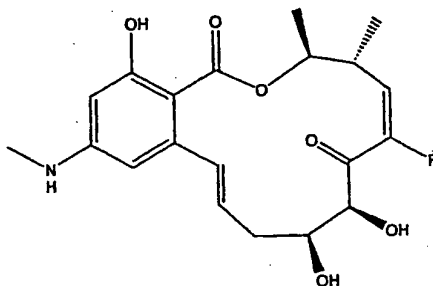
27. A compound having the structure:

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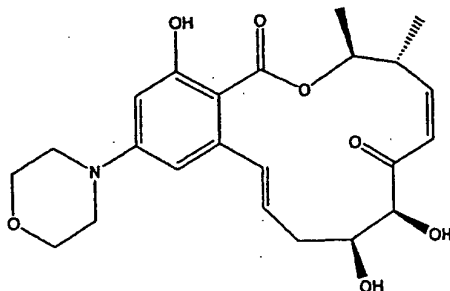
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

28. A compound having the structure:



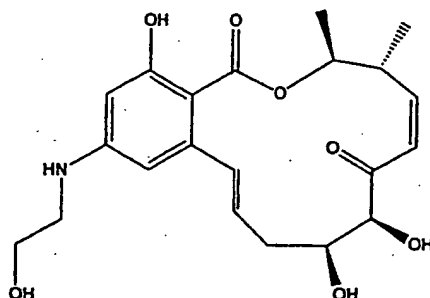
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

29. A compound having the structure:



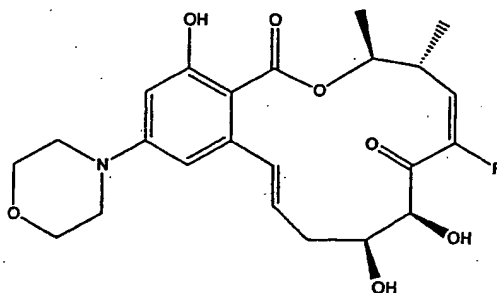
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

30. A compound having the structure:



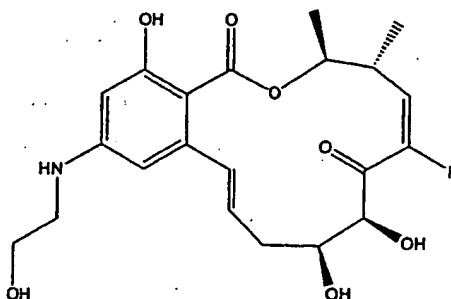
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

31. A compound having the structure:



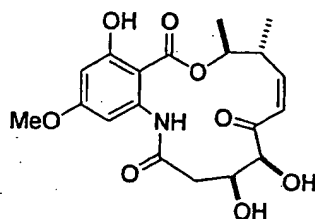
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

32. A compound having the structure:



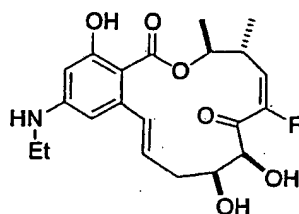
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

33. A compound having the structure:



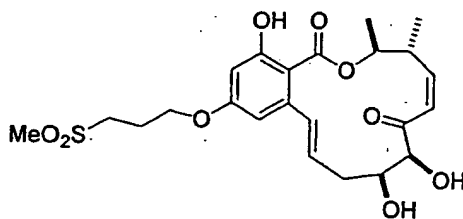
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

34. A compound having the structure:



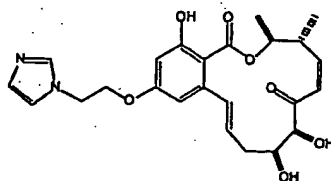
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

35. A compound having the structure:



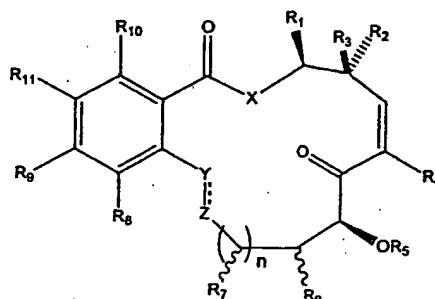
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

36. A compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

37. A pharmaceutical composition comprising:  
a compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(\text{alkyl})$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;


$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

Y is  $\text{CHR}_{17}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{17}$  or  $\text{NR}_{17}$ ; and Z is  $\text{CHR}_{18}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{18}$  or  $\text{NR}_{18}$ , wherein each occurrence of  $\text{R}_{17}$  and  $\text{R}_{18}$  is independently hydrogen or aliphatic, or  $\text{R}_{17}$  and  $\text{R}_{18}$  taken together is  $-\text{O}-$ ,  $-\text{CH}_2-$  or  $-\text{NR}_{19}-$ , wherein  $\text{R}_{19}$  is hydrogen or  $\text{C}_{1-6}$ alkyl, and Y and Z may be connected by a single or double bond; and

a pharmaceutically acceptable carrier;

with the proviso that when n is 1; X is O;  $\text{R}_1$  is methyl;  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_7$  and  $\text{R}_{11}$  are each hydrogen;  $\text{R}_5$  is hydrogen,  $\text{C}_{1-4}$ alkyl or  $-\text{C}(=\text{O})\text{C}_{1-4}$ alkyl;  $\text{R}_6$  is hydrogen, OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl; and  $\text{R}_9$  is OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $\text{R}_4$  is hydrogen;  $\text{R}_{10}$  and  $\text{R}_8$  are independently OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl; and Y-Z is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}=\text{CH}-$ ;
- (ii)  $\text{R}_4$  and  $\text{R}_8$  are each hydrogen;  $\text{R}_{10}$  is OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl; and Y-Z is  $-\text{CHR}^Y\text{CHR}^Z-$ ,  $-\text{CH}=\text{CH}-$  or ; wherein  $\text{R}^Y$  and  $\text{R}^Z$  are independently hydrogen,  $\text{C}_{1-4}$ alkyl or  $\text{C}_{1-4}$ alkanoyl; and

- (iii)  $\text{R}_4$  and  $\text{R}_{10}$  are each hydrogen, OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl;  $\text{R}_8$  is hydrogen, OH, halogen,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl; and Y-Z is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}(=\text{O})\text{CH}_2-$ .

38. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to inhibit NF- $\kappa$ B activation.

39. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to inhibit AP-1 activation.

40. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to inhibit a protein kinase.

41. The pharmaceutical composition of claim 39, wherein the protein kinase is MEKK1, MEK1, VEGFr or PDGFr.

42. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to inhibit proliferation of cancerous cells and angiogenesis on solid tumors.

43. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to have an anti-inflammatory effect.

44. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to treat psoriasis.

45. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to reduce skin photodamage.

46. The pharmaceutical composition of claim 37, wherein the compound is present in an amount effective to prevent restenosis.

47. The pharmaceutical composition of claim 37, where:

$R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(\text{alkyl})$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

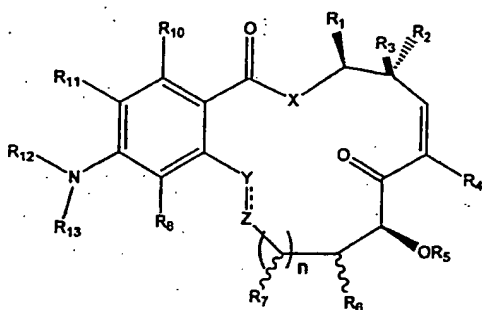
$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl,  $CH_2$  or S;

Y is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and Z is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $C_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and Y and Z may be connected by a single or double bond.

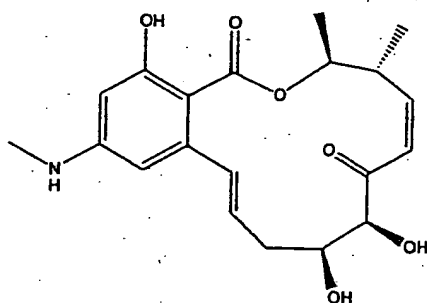
48. The pharmaceutical composition of claim 47, where X is oxygen and n is 1.
49. The pharmaceutical composition of claim 47, where  $R_4$  is halogen.
50. The pharmaceutical composition of claim 49, where  $R_4$  is fluorine.
51. The pharmaceutical composition of claim 47, where Y and Z together represent  $-CH=CH-$ .
52. The pharmaceutical composition of claim 51, wherein  $-CH=CH-$  is trans.



wherein  $R_1$ - $R_{13}$ ,  $n$ ,  $X$ ,  $Y$  and  $Z$  are as defined in claim 46, or

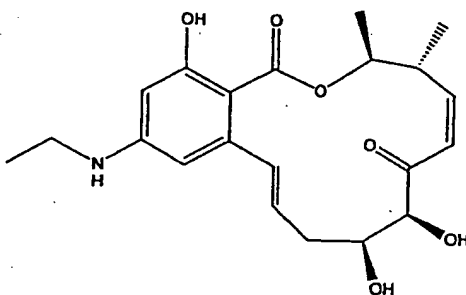
$R_{13}$  and  $R_8$  may, when taken together, form a cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydrogen, alkyloxy, amino, alkylamino, aminoalkyl, and halogen.

60. The pharmaceutical composition of claim 59, wherein  $X$  is oxygen and  $n$  is 1.
61. The pharmaceutical composition of claim 59, wherein  $R_4$  is halogen.
62. The pharmaceutical composition of claim 59, wherein  $Y$  and  $Z$  together represent  $-\text{CH}=\text{CH}-$ .
63. The pharmaceutical composition of claim 59, wherein  $R_1$  and  $R_2$  are each methyl and  $R_3$  is hydrogen.
64. The pharmaceutical composition of claim 59 wherein  $X$  is oxygen,  $n$  is 1,  $R_1$  and  $R_2$  are each methyl,  $R_3$  is hydrogen,  $R_4$  is halogen, and  $Y$  and  $Z$  together represent  $-\text{CH}=\text{CH}-$ .
65. The pharmaceutical composition of claim 63 or 64 wherein  $-\text{CH}=\text{CH}-$  is trans.
66. A pharmaceutical composition comprising:  
a compound having the structure:



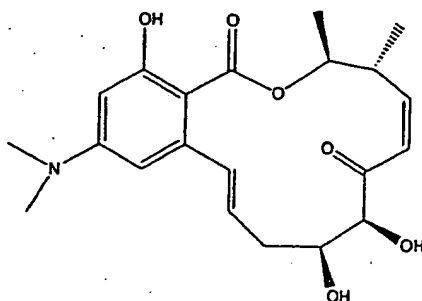
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising:  
a compound having the structure:



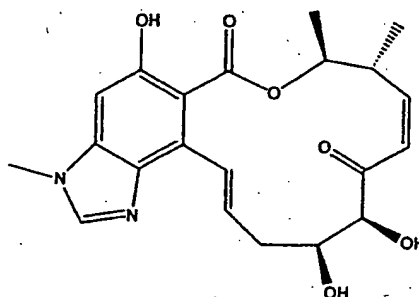
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising:  
a compound having the structure:



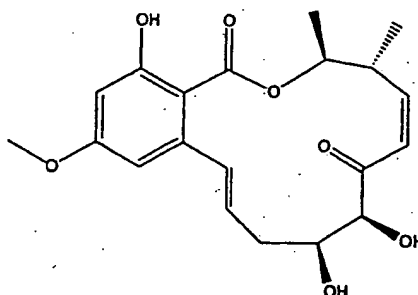
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

69. A pharmaceutical composition comprising:  
a compound having the structure:



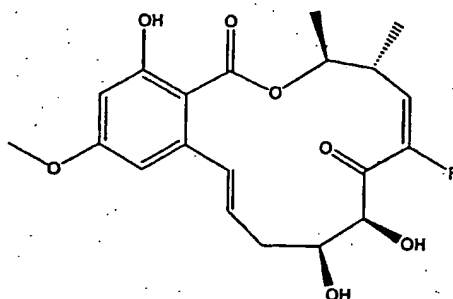
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

70. A pharmaceutical composition comprising:  
a compound having the structure:



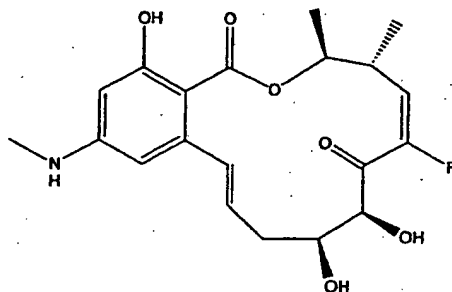
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

71. A pharmaceutical composition comprising:  
a compound having the structure:



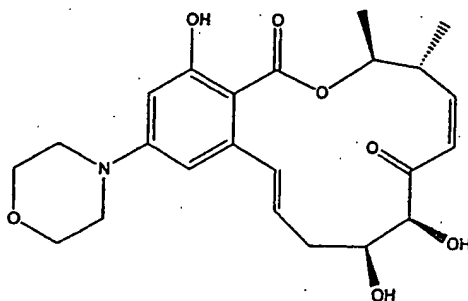
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

72. A pharmaceutical composition comprising:  
a compound having the structure:



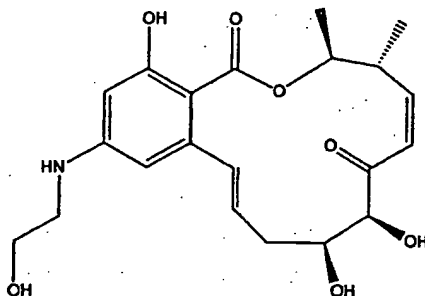
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

73. A pharmaceutical composition comprising:  
a compound having the structure:



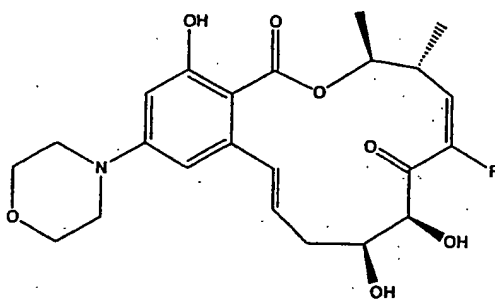
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

74. A pharmaceutical composition comprising:  
a compound having the structure:



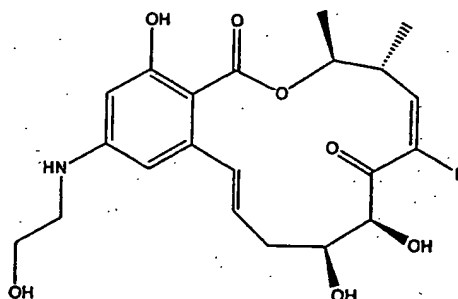
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

75. A pharmaceutical composition comprising:  
a compound having the structure:



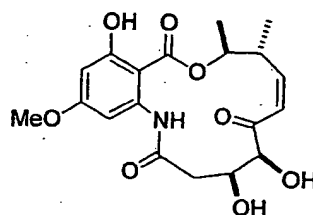
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

76. A pharmaceutical composition comprising:  
a compound having the structure:



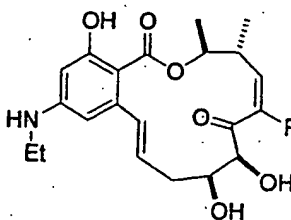
or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

77. A pharmaceutical composition comprising:  
a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

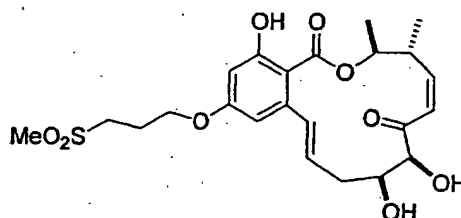
78. A pharmaceutical composition comprising:  
a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

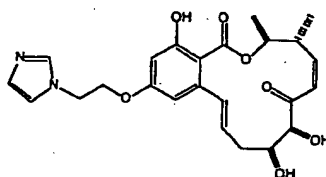
79. A pharmaceutical composition comprising:

a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

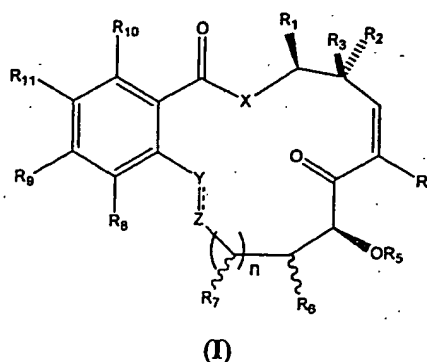
80. A pharmaceutical composition comprising:  
a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof; and  
a pharmaceutically acceptable carrier.

81. A topical pharmaceutical composition for preventing or treating UVB-induced  
photodamage comprising:

a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences

of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $C_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; and

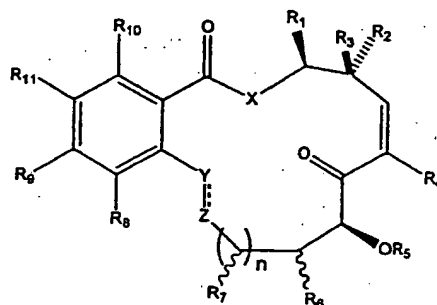
a pharmaceutically acceptable carrier;

wherein the compound is present in an amount effective to prevent or treat UVB-induced photodamage.

82. The pharmaceutical composition of claim 81, further comprising a cosmetic ingredient.

83. The pharmaceutical composition of claim 82, wherein the cosmetic ingredient is a sunscreen.

84. A method for treating an inflammatory and/or autoimmune disorder or a disorder resulting from increased angiogenesis and/or cell proliferation comprising:  
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or  $R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;


$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; and

a pharmaceutically acceptable carrier or diluent;

with the proviso that when  $n$  is 1;  $X$  is  $O$ ;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen,  $OH$ ,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $R_9$  is  $OH$ ,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; then one or more of the following groups do not occur simultaneously as defined:

- (i)  $R_4$  is hydrogen;  $R_{10}$  and  $R_8$  are independently  $OH$ ,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $Y-Z$  is  $-CH_2CH_2-$  or  $-CH=CH-$ ; and
- (ii)  $R_4$  and  $R_8$  are each hydrogen;  $R_{10}$  is  $OH$ ,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $Y-Z$  is  $-CHR^YCHR^Z-$ ,  $-CH=CH-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl; and

- (iii)  $R_4$  and  $R_{10}$  are each hydrogen,  $OH$ ,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_8$  is hydrogen,  $OH$ , halogen,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $Y-Z$  is  $-CH_2CH_2-$ ,  $-CH=CH-$  or  $-C(=O)CH_2-$ ; whereby the compound induces mRNA degradation and the method is for treating a disorder resulting from cell proliferation.

85. The method of claim 84, wherein the method is for treating a disorder selected from the group consisting of rheumatoid arthritis, psoriasis, asthma, cancer, sepsis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, and autoimmune disorders.

86. The method of claim 84, wherein the method is for treating rheumatoid arthritis.

87. The method of claim 84, wherein the method is for treating psoriasis.

88. The method of claim 84, wherein the method is for treating asthma.

89. The method of claim 84, wherein:

$R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

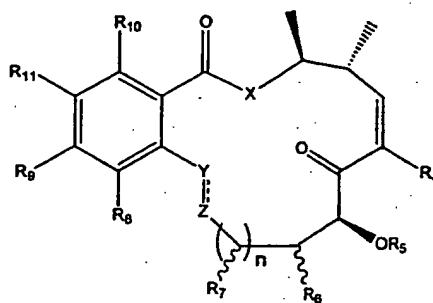
$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $C_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond.

90. The method of claim 89, wherein in the compound  $X$  is oxygen and  $n$  is 1.
91. The method of claim 89, wherein in the compound  $R_4$  is halogen.
92. The method of claim 89 is wherein in the compound  $R_4$  is fluorine.
93. The method of claim 89, wherein in the compound  $Y$  and  $Z$  together represent-  
 $CH=CH-$

94. The method of claim 93, wherein in the compound Y and Z together represent trans -CH=CH-.

95. The method of claim 89, comprising administering a compound wherein  $R_1$  and  $R_2$  are each methyl and  $R_3$  is hydrogen and the compound has the structure:



wherein  $R_4$ - $R_{11}$ ,  $n$ ,  $X$ ,  $Y$  and  $Z$  are as defined in claim 88.

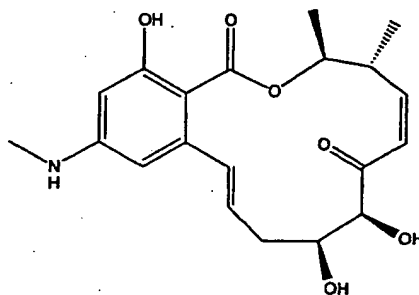
96. The method of claim 95, wherein in the compound  $X$  is oxygen and  $n$  is 1.

97. The method of claim 95, wherein in the compound  $R_4$  is halogen.

106. The method of claim 101, wherein in the compound X is oxygen, n is 1, R<sub>1</sub> and R<sub>2</sub> are each methyl, R<sub>3</sub> is hydrogen, R<sub>4</sub> is halogen, and Y and Z together represent -CH=CH-.

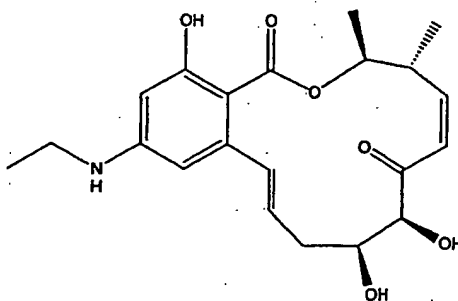
107. The method of claim 105 or 106, wherein in the compound -CH=CH- is trans.

108. The method of claim 84, comprising administering a compound having the structure:



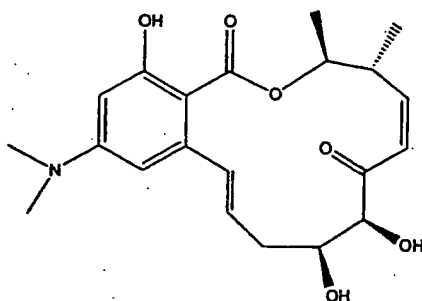
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

109. The method of claim 84, comprising administering a compound having the structure:



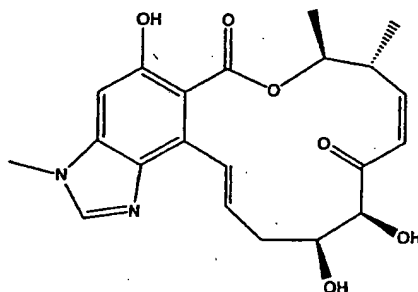
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

110. The method of claim 84, comprising administering a compound having the structure:



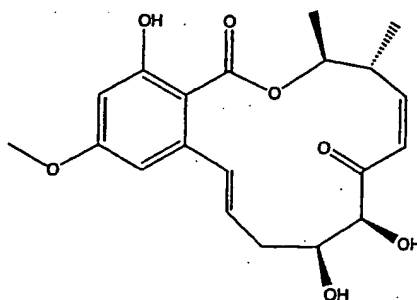
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

111. The method of claim 84, comprising administering a compound having the structure:



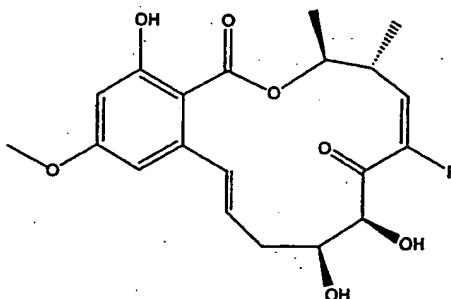
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

112. The method of claim 84, comprising administering a compound having the structure:



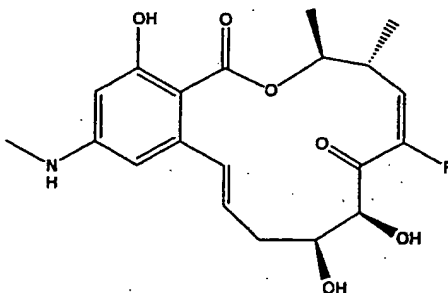
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

113. The method of claim 84, comprising administering a compound having the structure:



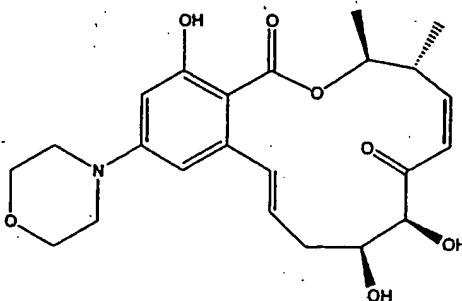
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

114. The method of claim 84, comprising administering a compound having the structure:



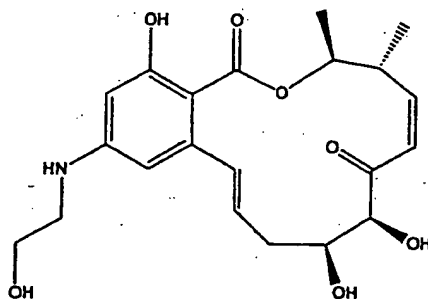
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

115. The method of claim 84, comprising administering a compound having the structure:



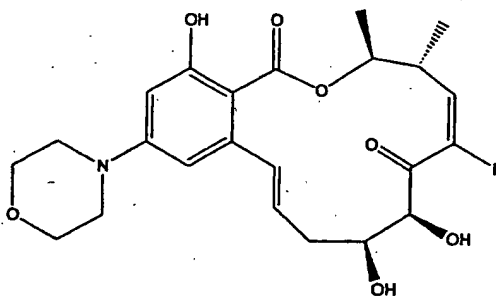
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

116. The method of claim 84, comprising administering a compound having the structure:



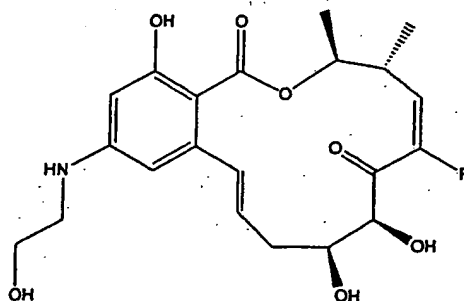
or pharmaceutically acceptable salt, ester, or salt of ester thereof.

117. The method of claim 84, comprising administering a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

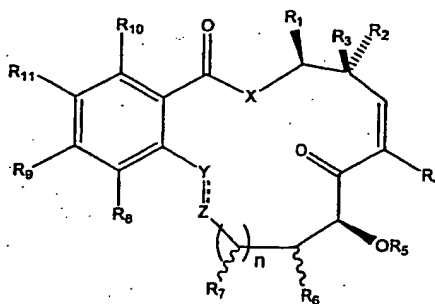
118. The method of claim 84, comprising administering a compound having the structure:



or pharmaceutically acceptable salt, ester, or salt of ester thereof.

119. A method for providing protection against UVB-induced photodamage to a subject, said method comprising:

Administering to the subject in need thereof a composition comprising a compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(alkyl)$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each

occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-\text{SO}_2(\text{R}_{16})$ , wherein  $\text{R}_{16}$  is an alkyl moiety, wherein one or more of  $\text{R}_{14}$ ,  $\text{R}_{15}$ , or  $\text{R}_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$\text{R}_8$  and  $\text{R}_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$\text{R}_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$\text{R}_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$\text{X}$  is absent or is O, NH, N-alkyl,  $\text{CH}_2$  or S;

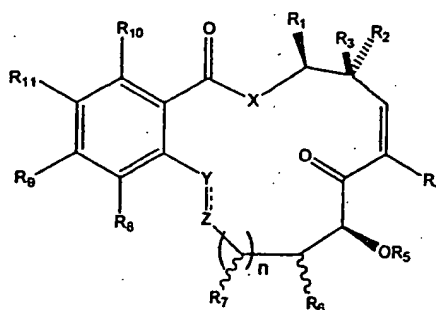
$\text{Y}$  is  $\text{CHR}_{17}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{17}$  or  $\text{NR}_{17}$ ; and  $\text{Z}$  is  $\text{CHR}_{18}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{18}$  or  $\text{NR}_{18}$ , wherein each occurrence of  $\text{R}_{17}$  and  $\text{R}_{18}$  is independently hydrogen or  $\text{C}_{1-6}$ alkyl, or  $\text{R}_{17}$  and  $\text{R}_{18}$  taken together is  $-\text{O}-$ ,  $-\text{CH}_2-$  or  $-\text{NR}_{19}-$ , wherein  $\text{R}_{19}$  is hydrogen or  $\text{C}_{1-6}$ alkyl, and  $\text{Y}$  and  $\text{Z}$  may be connected by a single or double bond; and  
a pharmaceutically acceptable carrier or diluent.

120. The method of claim 119, wherein in the step of administering, the composition is administered topically.

121. The method of claim 119, wherein the photodamage is skin wrinkles.

122. The method of claim 119, wherein the photodamage is a skin cancer.

123. A method for preventing or reducing the rate of restenosis, comprising:  
inserting a stent into an obstructed blood vessel, the stent having a generally tubular structure, the surface of the structure being coated with (or otherwise adapted to release) a composition comprising a compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(alkyl)$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

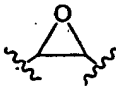
$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

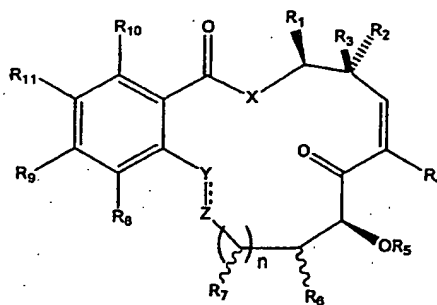
$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $C_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or  $C_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; and optionally a pharmaceutically acceptable carrier or diluent;

such that the obstruction is eliminated and the composition is delivered in amounts effective to prevent or reduce the rate of restenosis;

with the proviso that the following groups do not occur simultaneously as defined:  $n$  is 1;  $X$  is O;  $R_1$  is methyl;  $R_2, R_3, R_4, R_7, R_8$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_9$  and  $R_{10}$  are independently OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;

and  $Y-Z$  is  $-CHR^YCHR^Z-$ ,  $-\text{CH}=\text{CH}-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl.

124. A method for expanding the lumen of a body passageway, comprising:  
inserting a stent into the passageway, the stent having a generally tubular structure, the surface of the structure being coated with (or otherwise adapted to release) a composition comprising a compound having the structure:



(I)

or pharmaceutically acceptable salt, ester, or salt of ester thereof;

wherein  $R_1$  is hydrogen, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl; protected hydroxyl, straight or branched  $C_{1-6}$ alkyl, straight or branched  $C_{1-6}$ heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is  $C_{1-6}$ alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(alkyl)$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each

occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-\text{SO}_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is absent or is O, NH, N-alkyl,  $\text{CH}_2$  or S;

$Y$  is  $\text{CHR}_{17}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{17}$  or  $\text{NR}_{17}$ ; and  $Z$  is  $\text{CHR}_{18}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{18}$  or  $\text{NR}_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or  $\text{C}_{1-6}$ alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-\text{O}-$ ,  $-\text{CH}_2-$  or  $-\text{NR}_{19}-$ , wherein  $R_{19}$  is hydrogen or  $\text{C}_{1-6}$ alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; and optionally

a pharmaceutically acceptable carrier or diluent;

such that the passageway is expanded.

125. The method of claim 124, wherein the lumen of a body passageway is expanded in order to eliminate a biliary, gastrointestinal, esophageal, tracheal/bronchial, urethral and/or vascular obstruction.

126. The method of claim 125, wherein the lumen of a body passageway is expanded in order to eliminate a vascular obstruction.